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Letter to the Editors

Alzheimer's Disease and Aluminum Toxicology

Dear Editors:

A recent paper by C. N. Martyn and colleagues (*1*) appears to reinforce the environmental dismetabolic aluminum hypothesis of McLaclan (*2*), i.e., the involvement of abnormal aluminum (III) accumulation in the brain in the etiology of Alzheimer's disease (AD). Another recent review by Deary and Whelley (*3*) remarkably presents AD as a peculiar syndrome, which may represent the final result of diverse etiological factors.

The essential, only postmortem determined features of AD are *a*) senile plaques (i.e, neuronal degeneration areas, mainly of the cortex and hippocampus); *b*) neurofibrillary degeneration (proliferation of regular helix-shaped pairs of neurofilaments 10 nm in diameter, helically wound around each other with periodic twists 80 nm apart); and *c*) reduction of neurotransmitter activity, especially in the cholinergic system. Literature data and work carried out in these laboratories lend credit to the possible involvement of aluminum (III) in *all* three hallmarks of AD.

Senile Plaques

It is known that hippocampal membrane alterations occur in AD-affected patients (*4*), and it appears possible that the formation of senile plaques may just start with the degradation of the neuronal plasmatic membrane (*5*). In this connection, aluminum (III) may play a role by promoting membrane lipids peroxidation (*6,7*). Moreover, we find that the hydrolytically stable complex Al $(acac)_3$ (acac = 2,4-pentanedionate) is an effective chemical aggressor to the membrane of rabbit and rat erythrocytes (*8,9*), in that it causes osmotic fragility, extensive morphological defects (acanthocytosis), and a strong decrease in membrane fluidity (*9*). Human erythrocytes seem to be more resistant to aluminum (III), which causes, however, a significant modification in the membrane's protein configurations (*9*).

Neurofibrillary Degeneration

Many experiments *in vivo* based on the administration of Al(III) solution (*10*) succeeded in producing in the rabbit the proliferation of disorganized tangles of 10-nm diameter filaments, whose ultrastructure is similar to that of normal neurofilaments and whose pattern of immunocytochemical staining is similar to the pattern observed in AD (*11*). These observations are remarkable in that, on the one side, they lend credit to the supporters of the dismetabolic aluminum hypothesis, and on the other side, the specific morphologic features of the Al(III)-induced neurofibrillary degeneration were used by the opposers to the hypothesis for stressing that the nonhelix and nonpaired nature of the neurofilaments is a strong indication against any connection between an effect of Al(III) and AD.

In view of the great complexity of aqueous solution of Al(III) at pH 7.5 in the absence of strongly coordinating ligands (*12*), it has to be pointed out that all the experiments giving rise to anomalous neurofibrillary degeneration are based, in fact, on the administration of very poorly defined metal toxins. In this connection, toxicological experimentation *in vivo* and *in vitro* carried out in these laboratories is giving ample evidence that the speciation of the metal center is a crucial feature in directing the type of toxic effect of Al(III). Thus, $Al(acac)_3$ [neutral, octahedral, hydrolytically stable, and lipophilic (*13*)] and $Al(malt)_3$ (malt = 2-methyl-3-hydroxy-4-pironate) [neutral, octahedral, hydrolytically stable, and hydrophilic (*13*)] exhibit quite different toxicological behaviors (*14*), and they both behave quite differently with respect to aqueous aluminum lactate, for example, in their action on murine neuroblastomas (*15*).

It appears quite possible that the inability of Al(III) administration in inducing helixlike paired neurofilaments identical to those observed in AD may be the consequence of speciation effects and that a more tailored and appropriate choice of the coordination sphere of the metal toxin may eventually lead to the production of neurofibrillary tangles quite similar to those typical of AD.

Reduction of Neurotransmitter Activity

Postmortem neurochemical studies on AD patients demonstrated a severe loss of cortical neurotransmitters, particularly in the cholinergic synthetic enzymes activities (*16*) and to a lesser extent in several other cortical neurotransmitters systems such as somatostatinergic (*17*), serotoninergic (*18*), and noradrenergic (*19*) neurotransmitters. In model experiments, it was found that Al(III) inhibits choline transport in rat brain (*20*), in rat synaptosomes from cortex and hippocampus (*21*), and in human erythrocytes (*22*) and reduced neural choline acetyltransferase activity in the rabbit (*23*). The uptake of choline, glutamate, norepinephrine, and serotonin into rat synaposomes was also found to be inhibited by Al(III) (*20,24,25*). Moreover, in view of the critical relevance of the fluidity of neuronal membranes to the correct functioning of membrane receptors [especially those relevant

to serotonin (*26*)], it is possible that the influence of Al(III) on this cellular feature could eventually join two aspects of aluminum pathology, i.e, aggression to the plasmatic membrane and reduction of neurotransmitter activity.

In conclusion, we would like to stress the importance of thinking in terms of Al(III) speciation in biological, biochemical, and bioinorganic research. Thus, future experimentation should take in account *a*) the hydrolytic behavior of the metal center; *b*) the existence in solution of natural or artificial (designed) complexing agent; *c*) the thermodynamic stability and the kinetic behavior (lability-inertia) of the relevant adducts; *d*) the analytical concentration of both metal and ligands; and *e*) the lipophilic-hydrophilic character of the administered species.

Summary

The three hallmarks of Alzheimer's disease, i.e., senile plaques, neurofibrillary degeneration, and reduction in cholinergic activity, are evaluated as possible results of the aggression of dismetabolic Al(III) to relevant biological targets. Recent biological experimentation *in vivo* and *in vitro* supports such connection and stresses the dramatic importance of metal speciation in directing the pathological effects Al(III).

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